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EXPERIMENTS ON ALASTRIM.

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On account of some uncertainty as to the nature of an eruptive disease in the West Indies, inoculations have been performed at the Hygienic Laboratory of the United States Public Health Service in an attempt to determine its immunological relationship. The disease has been called alastrim, varioloid-varicella, and smallpox. Those who have not called the disease smallpox have been led to a different diagnosis primarily by its low death rate and the mildness or absence of the fever during the eruptive stage.

Accounts of the disease (1) (2) (3) (4) (5)[1] differ among themselves as much as any of them differ from what has been observed of the smallpox prevalent in the United States for the past 25 years. In general it is stated that the disease has been most prevalent among negroes and has tended to involve the more superficial layers of the skin in the vesicular stage, with relatively little primary umbilication, streptococcal infection, severe pustulation, or permanent scarring. Comparisons of its clinical immunology with that of accepted smallpox have been obscured by the nonrecognition of three facts: the acceleration of the reaction to inoculation of vaccine virus in immune individuals (6),[2] the frequent absence of complete immunity to vaccine virus after an attack of smallpox (7) (8) (9),[3] and the occasional absence of immunity to smallpox after successful vaccination or after an attack of smallpox itself (10) (11).[4]

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[1] (1) Dickson and Laselle. Varioloid-varicella in Trinidad: Jour. Trop. Med., 1903, **6**, 318.
(2) Clarke. Discussion of paper by Dickson and Laselle: Jour. Trop. Med., 1903, **6**, 320.
(3) Aragao. A propisto do alastrim: Brazil Medico, 1911, **9**, 941.
(4) Rudolph. Weisse Pocken: Münch. med. Wchnschr., 1911, **58**, 295.
(5) Melhorn. Smallpox in Haiti: U. S. Navy Med. Bull., 1921, **15**, 492.

[2] (6) Force. The Control of Smallpox: Modern Medicine, 1921, **3**, 177.

[3] (7) Bowen. Results of Revaccination in the British Army: Transactions Epidem. Soc. London, 1867, **2**, 230. (31.9 to 45.1 per cent of perfect pustules from vaccination of soldiers and recruits showing marks of previous smallpox.)

(8) Sinigar. Results of the Vaccination of 1,060 Adults: Lancet, 1902, **1**, 951. (89 per cent of pustules from vaccination of adults who gave evidence of previous smallpox.

(9) Force and Stevens. Responsibility of the Vaccinator in Overcoming the Rational Objections to Smallpox Vaccination: Journal Lab. and Clin. Med., 1918, **3**, 220. (62 per cent vaccinias or vaccinoids produced on vaccinating young adults who gave a history of previous smallpox.)

[4] (10) Schön. Die Blättern in Afrika und die Schutzpockenimpfung daselbst: Centralbl. f. Bakt., 1896, **20**, 641. (Repeated attacks of smallpox in negroes are not exceptional, and individuals who have had smallpox may be vaccinated later with success.)

(11) Seaton. Handbook of Vaccination, London, 1868, p. 185. (One per cent of the admissions to the smallpox hospital in London were second attacks. Some vaccinated persons may contract smallpox within a few weeks or months after vaccination.)

Our material was derived from two sources, through the courtesy of Prof. W. G. MacCallum, of Johns Hopkins University, and Lieut. Commander G. F. Clark of the Medical Corps of the United States Navy. In September, 1920, Prof. MacCallum visited Jamaica and investigated a number of cases of alastrim. In the course of his investigation he secured pustule contents from several of the patients. Portions of the material from these patients were mixed with 0.5 per cent phenol in saline solution and sealed in small test tubes. These tubes were brought to Baltimore and placed in cold storage. On March 21, 1921, two of these tubes were secured from Prof. MacCallum, brought to the Hygienic Laboratory in an iced container, and placed in storage at 5° C. On March 4, 1921, Lieut. Commander Clark, who was stationed in Haiti, mailed to the Hygienic Laboratory a sealed tube containing crusts from a patient having alastrim, together with some glass slides on which pustule contents had been dried. This material reached the laboratory on March 21, and was placed in storage at 5° C. With the material from these two sources the following experiments were performed.

Experiment I.

March 26, 1921: Two crusts from the Haitian patient were ground in a mortar with 12 drops of saline. A piece of sterile glass tubing, having an inside diameter of about 3 mm., was encircled by a file scratch and broken squarely off. Approximately 0.5 c. c. of the suspension of crusts was drawn up into the tube and transferred to the left side of the freshly shaved backs of two *Macacus rhesus* monkeys, the tube being held perpendicularly to the tightly drawn skin and rubbed vigorously to and fro while the suspension was released a drop or so at a time. The friction was continued until a distinct reddening of the skin was observed.

The two tubes containing pustule contents from two Jamaican patients (G and H) were centrifuged, opened, and the phenolized saline pipetted off. Enough fresh sterile saline was then added to each tube to give approximately a 1 in 10 suspension of pustule contents. The right side of the back of each monkey was similarly inoculated with these suspensions; the anterior portion with suspension G and the posterior portion with suspension H.

When observed one day after inoculation, the inoculated areas were covered with serum scabs resembling a thin layer of beeswax. Accompanying the scabs were a number of reddish scratches which healed rapidly. With the exception of a slight shrinking, no change occurred in the beeswaxlike scabs until nine days after inoculation, when the following conditions were observed:

Monkey 1.—Right side, anterior, inoculated with Jamaican suspension G: The scab had been picked off, revealing 13 lesions, 12 grouped and one at about 3 mm. distance. The lesion consisted of a reddish elevated base surmounted by a white circular summit having a depressed brownish center. The individual lesion measured 3 mm. in diameter. Right side, posterior, inoculated with Jamaican suspension H: The waxy scab was still adherent. Left side, inoculated with Haitian suspension: The waxy scab was off, revealing 5 scattered lesions similar to those of area "G."

Monkey 2.—Right side, anterior (Jamaican G): There was a group of seven lesions, one decidedly reddened from scratching. The scab was still adherent to area "H." The inoculation of the left side with Haitian alastrim scabs had been made by means of long irregular scratches which healed promptly. The site showed a chain of eight lesions rather more elevated than above described, but with white summits and depressed brown centers.

Eleven days after inoculation:

Monkey 1.—The lesions of the Jamaican G area were much increased in elevation and redness. The monkey had scratched off the whitish tops (vesicles) exposing crater-like depressions. Yellowish crusts were forming. The waxy scab was removed from the Jamaican H area showing perfectly smooth skin beneath. Evidently there had been no itching, which accounts for the persistence of the scab. The Haitian area was similar in appearance to Jamaican G, but the lesions were separate.

Monkey 2.—The lesions on all sites resembled lesions on the corresponding sites on Monkey 1.

The lesions on Monkey 1 were scraped and the scrapings ground with saline. The day following the curetting, reddish scabs formed, which dropped off on the 16th day, leaving crater-like pits. Circular brownish crusts formed on each lesion of Monkey 2, which were removed on the 13th day, exposing crater-like depressions containing a small amount of pus.

Results.—A vesico-papular eruption was produced by the inoculation of two monkeys with crusts from Haitian alastrim and pustule contents from Jamaican alastrim. This eruption was similar to that produced in three monkeys some months previously, inoculated by one of the authors (J. P. L.) with pustule contents from a case of smallpox occurring in the District of Columbia.

Experiment II.

Thirteen days after inoculation with alastrim material, the two monkeys and a normal control were inoculated as follows:

Monkey 1.—Inoculated with a highly potent vaccine virus in four needle scratches each about 3 cm. in length.

Monkey 2.—Reinoculated with the alastrim material (Jamaican G) which had produced an eruption on both monkeys. The material was rubbed in with glass tubes as described in the first experiment.

Monkey 4.—A normal animal was inoculated in seven needle scratches with the potent vaccine virus used on Monkey 1.

One day after inoculation:

Monkey 1.—The vaccination scratches were slightly elevated, but there was no redness.

Monkey 2.—A waxy scab had formed at the inoculation site.

Monkey 4.—The vaccination scratches had almost healed, there being no elevation or redness.

Three days after inoculation:

Monkey 1.—The scratches had healed, there being no elevation or redness.

Monkey 2.—No change.

Monkey 4.—No change.

Four days after inoculation:

Monkey 1.—Slight papule at end of one scratch.

Monkey 2.—No change.

Monkey 4.—The vaccination scratches showed distinct papules measuring 4 mm. across the line of scratch, with areolæ of 5 mm.

Five days after inoculation:

Monkey 1.—The scratches were no longer palpable.

Monkey 2.—Part of the waxy scab was removed, exposing a skin area slightly roughened, but with no signs of inflammation.

Monkey 4.—Vesicles were beginning to form on the summits of the papules.

Six days after inoculation:

Monkey 1.—No change.

Monkey 2.—All the waxy scab had come off, exposing two red spots 2 mm. in diameter, the rest of the area being smooth.

Monkey 4.—All seven scratches showed papules composed of overlapping circles with vesicles beginning at the summits.

Eight days after inoculation:

Monkey 1.—No change.

Monkey 2.—Small red spots fading.

Monkey 4.—There was definite vesicle formation over the entire papular area.

Ten days after inoculation:

Monkey 1.—No change.

Monkey 2.—There was a slight roughness of the skin as if papules had formed and disappeared.

Monkey 4.—Brownish scabs were beginning to form in the center of the vesicles.

Results.—A monkey successfully inoculated with Haitian and Jamaican alastrim was refractory to a strain of vaccine virus which gave a typical vaccinia in a normal monkey. A monkey successfully inoculated with Haitian and Jamaican alastrim was refractory to the same Jamaican alastrim.

Experiment III.

March 28, 1921: Rabbit A was shaved and inoculated with alastrim material (Jamaican G), 1 in 10 suspension on the right side, 1 in 50 on the left side. The technique was like that described for the inoculation of the monkeys with alastrim. Rabbit B was similarly inoculated with Jamaican H.

April 6, 1921: During the nine days following inoculation no eruption had appeared at any of the inoculated sites. Rabbit A was reinoculated with scrapings from the eruption produced by the Haitian crusts on Monkey 1. Rabbit B was reinoculated with scrapings from the eruption produced by Jamaican G pustule contents on Monkey 1. Three days after reinoculation a slight patchy erythema appeared on Rabbit A, which disappeared the next day. There was no change in the inoculated area on the other rabbit. The abrasions produced by the inoculation healed quickly.

April 15, 1921: Rabbit A was vaccinated with dilutions of a potent vaccine virus, a normal rabbit being used as a control. The area vaccinated with each dilution measured 2.5 by 5 cm. At the end of seven days a few accelerated lesions had developed and dried to tiny brown crusts. The control rabbit had typical seventh-day full vaccinia vesicles.

Rabbit A and control.

Dilution of vaccine virus.	Eruption on Rabbit A.	Eruption on normal rabbit.
1:1,000	21 discrete lesions	Confluent, covering 100 per cent of the inoculated area.
1:3,000	19 discrete lesions	95 per cent confluent.
1:10,000	5 discrete lesions	Do.
1:30,000	1 lesion	50 per cent confluent.

April 16, 1921: Rabbit B was vaccinated, using the same technique, virus, and dilutions as Rabbit A. A control was also vaccinated. The results seven days later were as follows:

Rabbit B and control.

Dilution of vaccine virus.	Eruption on Rabbit B.	Eruption on normal rabbit.
1:1,000	6 discrete lesions	Confluent, covering 75 per cent of the inoculated area.
1:3,000	3 discrete lesions	50 per cent confluent.
1:10,000	No lesions	40 per cent confluent.
1:30,000	do	5 discrete lesions.

Twenty other normal rabbits have been inoculated before and since with dilutions of this vaccine virus, using the same technique, and in none has the eruption been so accelerated or so scanty as that observed on Rabbits A and B.

Results: A rabbit (A) was inoculated cutaneously with alastrim pustule contents (Jamaican G), which had produced eruptions on two monkeys. No eruption was produced on the rabbit. Nine days later the rabbit was reinoculated cutaneously with scrapings from an eruption produced in a monkey by Haitian alastrim. A transient erythema was produced. Nine days after the reinoculation the rabbit was again inoculated cutaneously with dilutions of a potent vaccine virus and showed a few tiny scattered lesions which were definitely accelerated and had become crusted on the seventh day, at which time a confluent eruption on a control rabbit was at its height. The rabbit, was, therefore, almost completely immune to vaccine virus.

Another rabbit (B) was inoculated with alastrim pustule contents (Jamaican H) which produced no results on monkeys. No eruption was produced on this rabbit. Nine days later the rabbit was reinoculated with scrapings from an eruption produced on a monkey by Jamaican G alastrim. No eruption was produced. Ten days after the reinoculation, the rabbit was vaccinated with essentially the same results as in Rabbit A.

Two rabbits were therefore immunized to alastrim to such a degree that, though they showed no eruption, they were later observed to be almost completely immune to vaccine virus, the scanty lesions being in no sense imperfect in development but definitely accelerated, as in vaccinoid.

Experiment IV.

March 29, 1921: Six rabbits which had recovered from vaccinia, together with two normal controls, were inoculated intracutaneously with enough of the following materials to produce a 10 mm. bleb at each inoculation site: Suspensions (1:10) of smallpox crusts, chicken pox crusts, Jamaican G alastrim, Jamaican H alastrim, and vaccine virus, and enough Haitian alastrim vesicle contents (which had been received dry on slides) to make a suspension, when mixed with saline, comparable in turbidity with the other suspensions.

A positive immune reaction was taken to be indicated by the appearance of a reddened areola with a papule of at least 5 mm., which reached its height on the second or third day following inoculation. Both controls and one of the vaccinated rabbits were negative at all inoculation sites. The remaining rabbits were all negative to chicken pox and all positive to smallpox and vaccine virus. All gave very doutbful reactions to the Jamaican H strain of alastrim, the strain which had failed to produce eruptions on monkeys. Of four sites inoculated with Haitian alastrim, three showed positive reactions, and of three inoculated with Jamaican G alastrim, two were positive.

Two weeks later a second series of inoculations was performed, using three rabbits of the first series, three normal controls, and two other previously vaccinated rabbits. The material was the same as before except that suspensions of crusts from lesions produced on a monkey by Haitian and Jamaican G alastrim were substituted for the original (human) Haitian and Jamaican H materials. Fresh vaccine virus was also used. Possibly on account of the age of the material, negative or doubtful reactions were observed, except with the fresh vaccine virus. The chicken pox was, however, consistently negative.

Results: Smallpox crusts, vaccine virus, and alastrim material produced positive intracutaneous reactions in animals previously immunized to vaccine virus. Chicken pox did not produce such reactions.

Summary of Results.

A vesico-papular eruption was produced in monkeys by inoculation both with crusts and with vesicle contents from alastrim patients. The animals were protected against reinoculation with alastrim and vaccine virus. Rabbits inoculated with alastrim showed no eruption, but were almost completely immune to vaccine virus. Rabbits previously inoculated with vaccine virus gave positive intracutaneous reactions to smallpox crusts, alastrim material, and vaccine virus, but remained negative to chicken pox crusts.

The fact that definite immunity to vaccinia is produced by previous inoculation with alastrim is additional evidence of the essential identity of alastrim with smallpox.

INHALATION EXPERIMENTS ON INFLUENZA AND PNEUMONIA, AND ON THE IMPORTANCE OF SPRAY-BORNE BACTERIA IN RESPIRATORY INFECTIONS.[1]

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During the epidemic of influenza occurring in the winter season of 1919–20, the junior author was assigned by the Public Health Service to cooperate with the senior author in a study of this disease. The work was done in the Pathologic Institute of the University of Cincinnati. The institute is in direct connection with the Cincinnati General Hospital. This close association of the institute with the hospital presented a favorable opportunity for securing fresh

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[1] From the Laboratory of Bacteriology and Hygiene, University of Cincinnati, and the United States Public Health Service.

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[2] Detailed to the work by the United States Public Health Service.